REMARKS

1. STATUS OF THE CLAIMS

Claims 1-8, 10-17 and 21-36 are pending.

Claims 30-32 and 34-35 have been amended by canceling reference to non-elected SEQ ID NO:01. This amendment does not narrow the scope of any of the claims within the meaning of *Festo*,[1] because cancellation of non-elected invention in not related to a "statutory requirements for a patent" but rather is related to the Patent Office's convenience for organizing searches. Applicants reserve the right to prosecute the cancelled (or similar) claims in another application(s).

Claim 35 has been amended to correct a typographical error.

Claim 36 has been amended by changing "The plant tissue of Claim 34" to "The transgenic plant of Claim 34" to provide antecedent basis. Claim 36 has also been amended to recite that the transgenic plant tissue "comprises 12.5 fold higher level of lutein" as compared to lutein produced in a wild type plant tissue. Support is in the Specification's teaching that expressing the recited SEQ ID NO:4 polypeptide sequence in plants results in plant leaves with an increase of lutein from 8% of the amount of lutein in wild type Arabidopsis[2] to 100% of wild type levels.[3]

Claim amendments were made to describe particular embodiments of the invention, notwithstanding Applicants' belief that the cancelled and unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, but rather for the purpose of furthering Applicants' business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).[4]

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1 *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, U.S., No. 00-1543, 5/28/02.
2 Specification, page 45, lines 23-26, and Figure 3C.
3 Specification, page 45, lines 7-8, and Figure 3D.
4 65 Fed. Reg. 54603 (September 8, 2000).

2. WITHDRAWN REJECTIONS

Applicants note, with appreciation, that the Examiner withdrew the following objections and rejections:[5]

A. Objection to the title,[6]

B. Objection to Claims 22 and 33,

C. Rejection of Claims 33, 35 and 37 under 35 U.S.C. §112, second paragraph,

D. Rejection of Claims 1-8, 11-17, 21-25 and 30-36 under 35 U.S.C. §112, first paragraph (written description), and

E. Rejection of Claim 37 under 35 U.S.C. §112, first paragraph (enablement).

3. REJECTION OF CLAIMS 11-13, 16, 17, 21-30 AND 32-34 UNDER 35 U.S.C. §101 (UTILITY)

Claims 11-13, 16, 17, 21-30 and 32-34 were rejected under 35 U.S.C. §101 for allegedly lacking patentable utility.[7] Applicants respectfully traverse because the Examiner has not established a *prima facie* case of lack of utility. Furthermore, even if such a case were arguably made, it is rebutted by Applicant's evidence.

A. A *Prima Facie* Case Of Lack Of Utility Is Not Made

Under the law, "To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the *prima facie* showing."[8] However, this has not been done.

The Examiner argued that there is no "substantial utility" for complementing the mutant phenotype of the Arabidopsis lut1 mutant because this is a "very expensive wild-type-phenotype weed."[9] The Examiner also argued that using the recited nucleic acids as probes to identify

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5 Office Action, items 4-8 beginning on page 2.
6 Applicants note that the caption on the first page of this communication reflects the amended title "LUT1 gene from Arabidopsis and its use in engineering carotenoids metabolism in plants."
7 Office Action, page 3, item 9.
8 MPEP 2107.02, citing In re Gaubert, 524, F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975).
9 Office Action, page 3, last paragraph.

homologs "is not a specific utility."[10] Both arguments ignore utilities other than complementation and use as probes, as taught by the Specification. For example, the Specification teaches that:

> "The present invention also provides methods for using LUT1 genes, and LUT1 polypeptides; such methods include but are not limited to use of these genes to produce transgenic plants, to **produce lutein, to increase lutein, to decrease lutein, to alter carotenoid ratios**, to alter phenotypes, and for controlled **carotenoid production**. It is not meant to limit the present invention to alterations in lutein. In some embodiments, LUT1 **alters production of one or more of the following carotenoids, violaxanthin, antheraxanthin, zeaxanthin, neoxanthin, zeinoxanthin, and β-carotenes**."[11]

> "In other embodiments, LUT1 gene sequences are utilized to **alter carotenoid phenotype, and/or to control the ratio or levels of various carotenoids** in a host. In some embodiments, LUT1 sequences alter the **production of hydroxylated carotenes**. In yet other embodiments, LUT1 gene sequences are utilized to confer a carotenoid phenotype, and/or to decrease a carotenoid phenotype or to increase the production of a particular carotenoid, or to promote the production of novel carotenoid pigments. Examples are described U.S. Patent No. 6,524,811 to Cunningham, *et al.* (February 25, 2003), herein incorporated by reference. Thus, it is contemplated that nucleic acids encoding a LUT1 polypeptide of the present invention may be utilized to either increase or decrease the level of LUT1 mRNA and/or protein in transfected cells as compared to the levels in wild-type cells. Examples are described in U.S. Patent No. 6,642,021 ; U.S. Patent Appln. Pub. Nos. US 20020102631A1, US 20020086380A1 to Cunningham, Jr., *et al.*, (November 4, 2003; August 1, 2002, respectively), all of which are herein incorporated by reference)."[12]

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10 Office Action, page 4, 1st paragraph.
11 Specification, paragraph bridging pages 33-34.

> "Also described are methods for **identifying genes involved in lutein production or zeaxanthin production, and of the *lut1*, *lut1* mutants** and related CYP97 genes discovered through use of these methods. These *lut1* and *CYP97* related genes have been identified, cloned, and characterized including determination of functional abilities."[13]

Since the Examiner improperly ignored other utilities, a *prima facie* case of lack of utility is lacking.

B. Rebuttal Of A *Prima Facie* Case Of Lack Of Utility

Even if a *prima facie* case of lack of utility were arguably made, which it is not, it is rebutted by (1) the Specification's teachings of utility both *in vivo* and *in vitro*, and (2) the patent Office's issuance of patents to similar *in vivo* utility. This is further explained below.

1. The Specification Teaches That Proteins Expressed By The Recited Sequences Are Useful Both *In Vivo* And *In Vitro*

The Examiner argued that "there is no evidence that one of skill in the art can engineer a transgenic plant with a useful phenotype by using the claimed nucleic acids to express the claimed proteins."[14] This again ignores evidence to the contrary that is in the Specification. In particular, the Specification teaches that *Lut1-1* mutants that contained 8% of wild type lutein,[15] increased their level of production of lutein to wild type levels (*i.e.*, to 100% of wild type)[16] upon expression of the recited SEQ ID NO:4 This amounts to a **12.5 fold increase** in the level of lutein following expression of the recited polypeptide SEQ ID NO:4. In other words, this data demonstrates the **successful use** of the invention's sequences to increase lutein levels in plants that have low and/or undetectable levels of lutein. This utility is (a) specific because it relates to unique enzymatic activity of the recited sequences, (b) substantial because it has a real world application, and (c) credible because it is supported by data that was expressly taught in the

12 Specification, paragraph bridging pages 75-76.
13 Specification, page 36, last paragraph.
14 Office Action, page 3, last paragraph.
15 Specification, page 45, lines 23-26, and Figure 3C.

Specification and published in a **peer reviewed** scientific article in Tian *et al.* (2004).[17] Accordingly, a *prima facie* case of lack of utility is rebutted.

The Specification additionally teaches one of skill in the art that the recited sequences may also be used to express Lut1 proteins *in vitro*. For example, the recited nucleotide sequences may be used to express Lut1 proteins in a cell (including plant, *E. coli*, yeast, etc.), the expressed enzyme may then be purified, followed by its use *in vitro* to convert substrates that contain β-rings and/or ε-rings to carotenoids, such as lutein. In this regard, the Specification **expressly** refers to the purification of LUT1 polypeptides,[18] to exemplary methods for purification of the polypeptides such as by expressing the protein with fusion partners[19] (exemplified by glutathione-S-transferase[20] and poly-histidine[21]) followed by disruption of the transgenic cells by physical or chemical means.[22] The purified LUT1 proteins may then be used *in vitro* to convert substrates that contain β-rings and/or ε-rings to carotenoids, such as lutein, as disclosed in the Specification[23] using methods known in the art, such as Sun, *et al. J. Biol. Chem.* 271, 24349-24352 (1996); Tian, *et al. Plant Mol. Biol.* 47, 379-388 (2001). In view of the additional utility of the invention's nucleotide sequences *in vitro*, a *prima facie* case of lack of utility cannot stand.

2. Altering Carotenoid Levels Is A Well-Established Utility

The law is that issuance of other patents for the same utility as asserted by Applicants is evidence of a well-established utility.[24] In this regard, altering carotenoid levels is a well-established utility as evidenced by the Patent Office's issuance of prior patents directed to expressing nucleotide sequences for use in altering carotenoids. For example, the Examiner's

16 Specification, page 45, lines 7-8, and Figure 3D.
17 Tian *et al.* (2004) The Arabidopsis LUT1 locus encodes a member of the cytochrome P450 family that is required for carotenoid ε-ring hydroxylation activity." PNAS January 6, 2004 Vol 101:1, 402-407. This reference that was cited by the Examiner in connection with a rejection based on alleged non-enablement. Office Action, page 6, 2nd paragraph.
18 Specification, paragraph bridging pages 64-65.
19 Specification, paragraph bridging pages 62-63.
20 Specification, page 63, 3rd paragraph.
21 Specification, page 63, last paragraph.
22 Specification, page 74, last paragraph.
23 Specification, page 39, lines 19-23.

attention is respectfully drawn to U.S. Patent No. 6,524,811, issued on 2/25/2003,[25] and U.S. Patent No. 6,642,021, issued 11/4/2003,[26] that **claim** methods for expressing DNA sequences to produce carotenoids. Since the issued claims are directed to one of the utilities asserted by Applicants, *i.e.*, altering the production of at least one carotenoid in a host cell, this utility is well established. This rebuts a *prima facie* case of lack of utility, even if one were arguably made in the first place.

In view of the above, Applicants respectfully request withdrawal of the rejection of Claims 11-13, 16, 17, 21-30 and 32-34 under 35 U.S.C. §101 for allegedly lacking patentable utility.

4. REJECTION OF CLAIM 36 UNDER 35 U.S.C. §112, SECOND PARAGRAPH (INDEFINITENESS)

Claim 36 was rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite on the basis of lacking antecedent basis for the recitation "The plant tissue of Claim 34."[27] Appropriate correction has been made by changing that term to "The transgenic plant of Claim 34." Accordingly, withdrawal of this rejection is respectfully requested.

5. REJECTION OF CLAIMS 1-8, 10-17 AND 21-36 UNDER 35 U.S.C. §112, FIRST PARAGRAPH (ENABLEMENT)

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24 *In re Cortright*, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999) (A patent specification described using "Bag Balm " cow udder ointment on the human scalp to treat baldness. The PTO's rejection for lack of utility was overturned since the PTO had issued a number of patents for treating baldness)

25 U.S. Pat. No. 6,524,811 exemplary Claim 1 recites "A method of obtaining a compound derived from dimethylallyl pyrophosphate (DMAPP), wherein said compound derived from DMAPP is an isoprenoid, steroid, or carotenoid, the method comprising: (a) inserting into a host cell a vector comprising a heterologous nucleic acid sequence, which encodes a protein having isopentenyl pyrophosphate (IPP) isomerase activity, wherein the heterologous nucleic acid sequence is operably linked to a promoter; (b) expressing the heterologous nucleic acid sequence to produce the protein wherein the protein enhances the production of a compound derived from DMAPP relative to an untransformed host cell; (c) observing the host cell for a color change caused by the enhanced production of a compound derived from DMAPP; and (d) recovering the compound derived from DMAPP from the host cell."

26 U.S. Pat.No. 6,642,021 exemplary Claim 1 recites "A method of producing or altering the production of at least one carotenoid in a host cell, relative to an untransformed host cell, the method comprising: a) inserting into the host cell a vector comprising a heterologous plant nucleic acid sequence which encodes SEQ ID NO:2, wherein said heterologous plant nucleic acid sequence is operably linked to a promoter; and b) expressing the heterologous plant nucleic acid sequence to produce, enhance, reduce, or otherwise affect the production of carotenoids in the host cell."

Claims 1-8, 10-17 and 21-36 continue to be rejected under 35 U.S.C. §112, first paragraph for allegedly being non-enabled.[28] Applicants respectfully traverse for the reasons explained below.

A. The Specification, Prior Art, And Art Published After Filing Of The Instant Application Demonstrate That Expressing A Nucleotide Sequence That Encodes One Protein In A Carotenoid Biosynthetic Pathway Alters The Level Of One Or More Product Of The Pathway

The Examiner argued that "the main issue with regard to enablement of the instant invention" is that Applicants have "not provided any arguments about the unpredictability of expressing **one** component of a metabolic pathway in an attempt to increase the yield of a product of the pathway."[29] The Examiner cited Stephanopoulos *et al.* (1993) in support of her position that "metabolic engineering of biosynthetic pathways is highly unpredictable."[30]

At the outset, the Examiner is respectfully reminded that one need go no farther than the **Specification,** which provides **data** that demonstrate that expressing the recited SEQ ID NO:4 polypeptide sequence resulted in a **12.5 fold increase** in the level of the lutein product of the carotenoid pathway from 8% of the amount of lutein in wild type Arabidopsis[31] to 100% of wild type levels.[32] This evidence refutes the Examiner's assertion.

Importantly also, this data was published in a **peer-reviewed** article by Tian *et al.* (2004).[33] Tian *et al.* taught that the recited SEQ ID NO:4 LUT1 protein has both β-ring hydroxylase activity and ε-ring hydroxylase activity, as follows:

"Several independent lines of evidence confirm that the *Arabidopsis* ε-**hydroxylase**/*LUT1* locus is a cytochrome P450 monooxygenase"[34] ". . . LUT1

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27 Office Action, page 4, item 10.
28 Office Action, page 5, item 11.
29 (Emphasis added) Office Action, page 11, last paragraph.
30 Office Action, page 71st paragraph, and paragraph bridging pages 11-12.
31 Specification, page 45, lines 23-26, and Figure 3C.
32 Specification, page 45, lines 7-8, and Figure 3D.
33 Tian *et al.* (2004) The Arabidopsis LUT1 locus encodes a member of the cytochrome P450 family that is required for carotenoid ε-ring hydroxylation activity." PNAS January 6, 2004 Vol 101:1, 402-407.
34 (Emphasis added) Tian *et al.*, sentence bridging pages 405-406.

also has **β-ring hydroxylation activity** *in vivo* (Table 1).[35]

Thus, the above disclosure in a **peer-reviewed** article squarely refutes the Examiner's disparagement of the asserted enzymatic activity of the recited SEQ ID NO:4 when she states that the instant application "**speculates** that SEQ ID NO:5 encodes a cytochrome P450 enzyme with β-ring hydroxylase and ε-ring hydroxylase activity that is involved in carotenoid biosynthesis."[36] The Examiner is respectfully reminded that she cannot substitute her unsupported opinion for the opinion of those skilled in the art who reviewed the Specification's same data that was also taught in Tian *et al.*, and who arrived at a conclusion that is opposite from that arrived at by the Examiner.

Applicants also note that Stephanopoulos *et al.* that was cited by the Examiner is an outdated reference that was published **11 years before** the instant application's filing date. Also, Stephanopoulos *et al.* does not speak specifically to carotenoid synthetic pathway. Importantly, Stephanopoulos *et al.*'s disclosure is squarely contradicted by the more recent and contemporaneous publication of prior art U.S. Patent No. 6,524,811, issued on 2/25/2003,[37] and U.S. Patent No. 6,642,021, issued 11/4/2003,[38] both of which contain **claims** that recite that expressing a DNA sequence encoding **one** enzyme in the **carotenoid biosynthetic pathway** alters the levels of one or more carotenoid products. The Examiner is respectfully reminded that U.S. patents are **presumed enabled**, and that

> "'[A]ny party making the assertion that a U.S. patent specification or claims fails, for one reason or another, to comply with §112 bears the burden of persuasion in

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35 (Emphasis added) Tian *et al.*, page 405, 2nd column, 1st full paragraph.

36 (Emphasis added) Office Action, page 6, last paragraph.

37 U.S. Pat. No. 6,524,811 exemplary Claim 1 recites "A method of obtaining a compound derived from dimethylallyl pyrophosphate (DMAPP), wherein said compound derived from DMAPP is an isoprenoid, steroid, or carotenoid, the method comprising: (a) inserting into a host cell a vector comprising a heterologous nucleic acid sequence, which encodes a protein having isopentenyl pyrophosphate (IPP) isomerase activity, wherein the heterologous nucleic acid sequence is operably linked to a promoter; (b) expressing the heterologous nucleic acid sequence to produce the protein wherein the protein enhances the production of a compound derived from DMAPP relative to an untransformed host cell; (c) observing the host cell for a color change caused by the enhanced production of a compound derived from DMAPP; and (d) recovering the compound derived from DMAPP from the host cell."

38 U.S. Pat.No. 6,642,021 exemplary Claim 1 recites "A method of producing or altering the production of at least one carotenoid in a host cell, relative to an untransformed host cell, the method comprising: a) inserting into the host cell a vector comprising a heterologous plant nucleic acid sequence which encodes SEQ ID NO:2, wherein said heterologous plant nucleic acid sequence is operably linked to a promoter; and b) expressing the heterologous plant nucleic acid sequence to produce, enhance, reduce, or otherwise affect the production of carotenoids in the host cell."

showing said lack of compliance."[39]

Since U.S. patents are presumed enabled, and since U.S. Patent Nos. 6,524,811 and 6,642,021 demonstrate that expressing a nucleotide sequence that encodes **one** protein in a carotenoid biosynthetic pathway alters the level of one or more product of the pathway, this refutes the examiner's assertion of non-enablement.

In addition, each of U.S. Patent Appln. Pub. No. US 20020102631A1 (published on 11/4/2003) and U.S. Patent Appln. Pub. No. US 20020086380A1 (published on 8/1/ 2002) provide **data** that demonstrate that expressing a DNA sequence encoding **one** enzyme in the **carotenoid biosynthetic pathway** alters the levels of one or more carotenoid products. This also refutes both the Examiner's position and the outdated disclosure of Stephanopoulos *et al.*

B. The Specification, Combined With The Prior Art, Provides Sufficient Guidance On How To Determine Enzyme Activity

The Examiner also argued that the "specification does not disclose any enzyme assays showing that the protein encoded by SEQ ID NO:5 has any specific enzymatic function."[40] However, the law does not require disclosure of such assays, but only a **"reasonable amount of guidance"** on how to carry out such assays.

> "Even a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides a **reasonable amount of guidance** on the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."[41]

Such guidance is provided by the Specification's teaching of the use of the exemplary prior art enzyme assays for β-hydroxylase activity and ε-hydroxylase activity.[42] This satisfies enablement.

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39 *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993).

40 Office Action, apge 6, 2nd paragraph.

41 (Emphasis added) *Ex parte Forman*, 230 USPQ 546 (BPAI 1986); *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App. 1982); *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988).

42 Specification, page 39, lines 19-23, referring to Sun, *et al. J. Biol. Chem.* 271, 24349-24352 (1996) and Tian, *et al. Plant Mol. Biol.* 47, 379-388 (2001).

C. The Prior Art Provides Methods For Successful Expression Of P450 Proteins In Yeast

The Examiner argued that, with specific reference to Claims 11 and 14, "subsequent experimental work was unsuccessful in providing an assay for enzymatic function" since Tian *et al.* (2004) disclosed that "initial attempts to express and assay LUT1 protein in yeast were unsuccessful."[43] However, it is important to note that Tian *et al.* stated that these were "**initial**" attempts. This does not negate enablement since

> "the mere possibility of inclusion of inoperative . . . [subject matter] does not prevent allowance of broad claims . . . "[44]

The prior art provides several approaches for successfully expressing P450 enzymes in yeast, such as those disclosed in the following exemplary prior art references (copies enclosed):

- Sugiura M *et al.* "Cloning and expression in Escherichia coli and Saccharomyces cerevisiae of a novel tobacco cytochrome P-450-like cDNA," Biochim Biophys Acta. 1996 Sep 11;1308(3):231-40,
- Bak S & Feyereisen R. "The involvement of two p450 enzymes, CYP83B1 and CYP83A1, in auxin homeostasis and glucosinolate biosynthesis," Plant Physiol. 2001 Sep;127(1):108-18,
- Cahoon EB *et al.* "Transgenic production of epoxy fatty acids by expression of a cytochrome P450 enzyme from Euphorbia lagascae seed," Plant Physiol. 2002 Feb;128(2):615-24,
- Collu G *et al.* "Geraniol 10-hydroxylase, a cytochrome P450 enzyme involved in terpenoid indole alkaloid biosynthesis,' FEBS Lett. 2001 Nov 16;508(2):215-20,
- Bertea CM *et al.* "Demonstration that menthofuran synthase of mint (Mentha) is a cytochrome P450 monooxygenase: cloning, functional expression, and characterization of the responsible gene," Arch Biochem Biophys. 2001 Jun 15;390(2):279-86, and
- Nair RB *et al.*, "Arabidopsis CYP98A3 mediating aromatic 3-hydroxylation. Developmental regulation of the gene, and expression in yeast," Plant Physiol.

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43 office Action, apge 6, 2nd paragraph, referring to Tian *et al.*, PNAS 101, 402-407 at page 405, 1st column.
44 *Application of Cook*, 939 F.2d 730, 169 USPQ 298 (CCPA 1971).

2002 Sep;130(1):210-20.

Since the prior art teaches methods for successful expression of P450 enzymes in yeast, the claims are enabled.

D. The Prior Art Provides Methods For Successful Expression Of P450 Proteins In Prokaryotic Cells

The Examiner argued that "expression in bacteria is highly unlikely to work given the problems of expression [of] eukaryotic membrane proteins in prokaryotic systems (See Hannig et al TIBTECH (1998) vol, 16, "focus", see second to last page, right column."[45] However, Hannig *et al.* that is relied upon by the Examiner is an outdated reference that was published **6 years prior** to the filing date of the instant application. Moreover, the disclosure of Hannig *et al.* is contradicted by later-published prior art references that show several approaches for successfully expressing P450 enzymes in prokaryotes (*e.g., E. coli*), such as those disclosed in the following exemplary prior art references (copies enclosed):

- Wittstock U & Halkier BA, "Cytochrome P450 CYP79A2 from Arabidopsis thaliana L. Catalyzes the conversion of L-phenylalanine to phenylacetaldoxime in the biosynthesis of benzylglucosinolate," J Biol Chem. 2000 May 12;275(19):14659-66,
- Bertea CM *et al.* "Demonstration that menthofuran synthase of mint (Mentha) is a cytochrome P450 monooxygenase: cloning, functional expression, and characterization of the responsible gene," Arch Biochem Biophys. 2001 Jun 15;390(2):279-86, and
- Hansen CH *et al.* "Cytochrome p450 CYP79F1 from Arabidopsis catalyzes the conversion of dihomomethionine and trihomomethionine to the corresponding aldoximes in the biosynthesis of aliphatic glucosinolates," J Biol Chem. 2001 Apr 6;276(14):11078-85. Epub 2000 Dec 22.

Since the prior art teaches methods for successful expression of P450 enzymes in prokaryotes, the claims are enabled.

E. The Specification's Working Examples Provides Evidence Of Protein Expression And Of Altered Lutein Levels

The Examiner argued that the claims lack enablement because the Specification "has not provided any working examples of expression of SEQ ID NO:5 in a healthy wild-type plant to demonstrate that is an effect on carotenoid metabolism."[46] However, none of the claims requires that (although they include within their scope) a plant that is transformed with the recited sequences be a "wild-type plant." Therefore, the Examiner's insistence of such showing is in error.

Moreover, the Examiner appears to improperly narrowly view the results in the Specification (which were also subsequently published in Tian *et al.* (2004)) by stating that the nucleotide sequence encoding the recited SEQ ID NO:4 has the "ability to **complement** the *lut1* mutation in Arabidopsis"[47] However, the data in Example 5, beginning on page 103 of the Specification, demonstrate that expression of SEQ ID NO:5 that encodes the recited SEQ ID NO:4 in plants resulted in a **12.5 fold increase** in the level of lutein produced by the plants.

Thus, the Examiner's narrow interpretation of the data and her improper requirement for expression in wild-type plants do not establish non-enablement.

45 Office Action, apge 6, 2nd paragraph.
46 Office Action, apge 7, 2nd paragraph.
47 (Emphasis added) Office Action, apge 5, last paragraph.

F. The Examiner's Insistence Of A "Guarantee" Is Improper

The Examiner argued that "there is no **guarantee** that one of skill in the art would be successful in expressing a polypeptide with as little as 72% identity to SEQ ID NO:4 to produce a recombinant protein with monooxygenase P450 activity."[48] However, enablement does not requires a "guarantee." All that is required is "a **reasonable amount of guidance"** [49] by the Specification on how to determine whether a sequence that has the recited "at least 72% identity" to SEQ ID NO:4 also possesses the recited "monooxygenase P450 activity." This is indeed the case in view of the Specification's teaching of prior art methods to determine such enzyme activity.[50]

G. The Examiner's Dismissal Of Applicants' Evidence Of Quinlan *et al.* Is In Error

The Examiner asserted that Quinlan *et al.*,[51] which was previously submitted to the Office by Applicants in support of enablement, was not persuasive for 3 reasons. First, the Examiner argued that "applicant elected SEQ ID NO:4 for prosecution" and that therefore SEQ ID NO:16 whose expression was demonstrated in Quinlan *et al.* is unpersuasive.[52] This argument improperly **ignores the scope of the claims,** which is not limited to SEQ ID NO:4, but also includes "a polypeptides at least 72% identical to SEQ ID NO:4." SEQ ID NO:16 has 78% identity with the recited SEQ ID NO:4 and therefore **falls within the scope of the claims.** Quinlan shows that expression of SEQ ID NO:16 "resulted in a change in carotenoid production from the bacteria"[53] expressing it. This is persuasive evidence that sequences falling within the scope of the claims have the recited activity. The Examiner's dismissal of this evidence is improper.

Second, the Examiner argued that "Quinlan *et al.* utilized a **complicated** system of expressing SEQ ID NO:16 in a pCOLADuet vector in BL21 (DE3) cells along with a second

48 Office Action, page 8, 1st paragraph.
49 *Ex parte Forman*, 230 USPQ 546 (BPAI 1986); *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App. 1982); *In re Wands*, 8 USPQ2d 1400, 1404 (CAFC 1988).
50 Specification, page 39, lines 19-23.
51 Quinlan *et al.* (2007) Archives of Biochemistry and Biophysics 458:146-157.
52 Office Action, apge 9, last paragraph.
53 Declaration by Dr. Dean DellaPenna, filed May 18, 2007.

plasmid encoding the Arabidopsis lycopene ε cyclase."[54] However, the law is clear that the

> "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[55]

Quinlan *et al.* used commercially available vectors. This is not undue experimentation.

Third, the Examiner argued that the "specification did not provide this type of detailed guidance about how to successfully express a monooxygenase in E. Coli; and Quinlan et al did not publish their work until after the instant Application was filed."[56] However, neither of these facts negates enablement because the **Specification** provides other methods for expressing the recited sequences (*e.g.*, Example 5), and the **prior art** is replete with a plethora of systems for expression of P450 membrane proteins in yeast (see item 5.C. *supra*) and prokaryotic cells (see item 5.D. *supra*).

Based on the above, Applicants respectfully assert that the teachings of Quinlan *et al.* are not only relevant, but also persuasive with respect to enablement of the entire scope of the claims.

In sum, Applicants respectfully request withdrawal of the rejection of Claims 1-8, 10-17 and 21-36 under 35 U.S.C. §112, first paragraph for allegedly being non-enabled.

CONCLUSION

Applicants respectfully requests reconsideration of the application in view of the above, which places the claims in condition for allowance.

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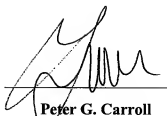
54 (Emphasis added) Office Action, sentence bridging pages 9-10.

55 *In re Certain Limited Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd *sub nom., Massachusetts Institute of Technology v. A.B. Fortina*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

56 Office Action, page 10, 1st paragraph.

Dated: February 17, 2009



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